

Conferences and Reviews

Colorectal Cancer

A New Look at an Old Problem

Discussant

NEIL W. TORIBARA, MD, PhD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER A. BOUSHEY, MD*: *Colorectal cancer is a highly prevalent health problem. The combined factors of a long natural history, familial susceptibility, and endoscopic accessibility of this malignant disorder and its precursor lesions offer a unique opportunity to understand the molecular genetics involved in the pathogenesis of colorectal cancer and to develop techniques and strategies for its early detection and prevention. Recent progress toward the realization of these goals has been exciting and is reviewed in this conference by Neil Toribara, MD.*

NEIL W. TORIBARA, MD, PhD†: Colorectal cancer is a major health problem in the United States. Cancer is the second leading cause of death in this country, behind only atherosclerotic cardiovascular disease, and colorectal cancer is the second leading cause of death from malignant neoplasms. This year an estimated 157,000 cases will be diagnosed and 56,000 deaths will result from colorectal cancer. The lifetime probability of colon cancer developing is approximately 1 in 15, or about 6%. Despite major advances in diagnostic and therapeutic technology, new understanding of some of the molecular changes occurring during colorectal carcinogenesis, and the inclusion of some form of screening in the health maintenance programs of many patients, the mortality from this disease remains high at slightly less than 50%.¹

In this discussion I will briefly outline our current understanding of etiologic factors in colorectal cancer and the prognosis of this disease with current therapy and follow with a more detailed account of two areas in which important advances are being made, molecular pathogenesis and early detection.‡

*Professor and Vice Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Assistant Professor, Department of Medicine, UCSF School of Medicine, and Research Associate, Department of Veterans Affairs, San Francisco.

‡See also the editorial by D. J. Ahnen, MD, "How to Capture a Revolution," on pages 523-525 of this issue.

Etiologic Factors

Epidemiologic and experimental studies suggest that factors involved in the development of colorectal cancer can be divided into exogenous and endogenous categories. The exogenous factors include environmental toxins and dietary components, and the endogenous factors include oncogenes or tumor suppressors and possibly metabolic abnormalities.

The effect of environmental elements is evident when the rate of colorectal cancer development is examined in populations migrating from a region with low rates to a region with a high rate.² Figure 1 shows the incidence of colon cancer in the Japanese population and the United States white population at age 60.^{2,3} The issei (the emigrants to the United States) had an incidence that is higher than that of their Japanese counterparts, but considerably lower than that of the white population. But the nisei, the first generation to be born and raised in the United States, acquired essentially the same incidence of colorectal cancer as that of the indigenous whites. Similar statistics have been reported in European emigrants to the United States and Polish emigrants to Australia.⁴ The rapid acquisition of this higher rate of colorectal cancer development is almost certainly due to environmental or dietary factors, or both.

A number of dietary elements have been suggested, some of which are listed in Table 1. The protective effects of fiber may be a combination of decreasing the transit time of intestinal contents, diluting and binding of possible toxins, and complex alterations of the bacterial biochemical milieu. These have the net effect of decreasing the amount of biologically active possible carcinogens available and their contact time with the bowel mucosa.⁵ High fat intake has also been associated with an increased risk for colorectal cancer, possibly by inducing increased amounts of bile acid synthesis. These bile acids are metabolized by bacteria in the colon to secondary bile acids that, although they themselves are

ABBREVIATIONS USED IN TEXT

FAP = familial adenomatous polyposis
FOBT = fecal occult blood test
HNPCC = hereditary nonpolyposis colon cancer

not carcinogenic, potentiate the effects of carcinogens.⁶ Experimental evidence suggests that calcium,⁷ folate,⁸ fish oil,⁹ and vitamins A, C, and E^{10,11} may have protective effects against the development of colorectal cancer. Recently reports have suggested that patients on a low-dose aspirin regimen had a substantially lower rate of colon cancer development than controls.^{12,13} This, along with reports of the efficacy of sulindac in causing polyp regression in some patients with familial polyposis,¹⁴ suggests that an inhibition of prostaglandin synthesis may protect against the development of cancer.

The endogenous or genetic factors vary widely in their contribution to the genesis of colorectal cancer. In some polyposis syndromes and cases of hereditary non-polyposis colon cancer (HNPCC) that include kindreds with colon cancer alone (Lynch syndrome type I) and colon cancer as part of a spectrum of malignant neoplasms (Lynch syndrome type II), the colorectal cancer inheritance is autosomal dominant and the genetic contribution is clear.^{15,16} Even in patients with relatives who have had either colon cancer or adenomatous polyps, however, the risk of colorectal neoplasms developing is greater than in an age-matched population, depending on the number of relatives, the degree of relatedness, and the age of onset of the disease in those relatives.

Prognosis of Colorectal Cancer With Current Therapy

Figure 2 shows the distribution of colorectal cancers. Over the past several decades, a relative shift has occurred in the distribution of these cancers toward the proximal colon that has made progressively fewer of these lesions accessible to digital rectal or rigid sigmoidoscopic examination. About 60% of colon cancers are distal to the splenic flexure and thus within the reach of a 60-cm flexible sigmoidoscope.¹⁷ In patients with HNPCC, however, about 70% of the cancers will be proximal to the splenic flexure, making flexible sigmoidoscopy inadequate as a surveillance method.

The prognosis of patients with colon cancer depends on the stage at diagnosis. The most commonly used systems are modifications of the staging proposed by Cuthbert Dukes in 1932. Table 2 shows the Turnbull modification¹⁸ of the Dukes' staging system for colorectal carcinomas along with five-year survival rates.¹⁹⁻²² A malignant lesion confined to the mucosa is known as carcino-

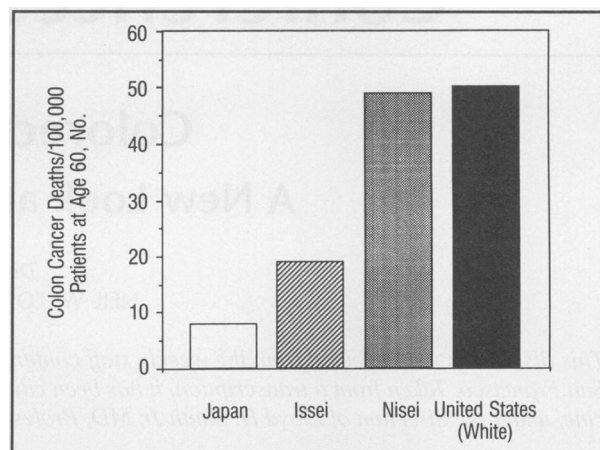


Figure 1.—Japanese emigrants to the United States (issei) have a higher incidence and mortality from colon cancer than the Japanese in Japan. The first generation born and raised in the United States (nisei) has acquired the same colon cancer incidence and mortality as the US white population (data from Haenszel and Kurihara²; adapted by permission from Daniel Podolsky, MD, and Milner-Fenwick Company³).

ma in situ. Because there are no lymphatics within the mucosa, these lesions are thought to have no metastatic potential, and therefore surgical or endoscopic excision (when possible) of these lesions is considered to be curative. Invasive cancers are staged according to their degree of penetration through the bowel wall (stages A and B), spread to local lymph nodes (stage C), and the presence of distant metastases (stage D). The survival statistics for patients with stage C2 or D lesions may improve in the future, however. Recent studies showed that about 65% of patients with stage C lesions treated with surgery and the chemotherapeutic combination of fluorouracil and levamisole hydrochloride were disease-free five years after diagnosis.²³ A number of studies have reported success in surgically treating isolated hepatic and pulmonary metastases. Only a few patients with stage D disease are candidates for such treatment, however.²⁴ Studies have not shown a significant advantage in treating rectal cancers with fluorouracil and levamisole, and patients are usually given irradiation combined with adjuvant fluorouracil.

Pathogenesis of Colorectal Cancer

Carcinogenesis is thought in most cases to be a multistep process, with the first step involving the acquisition of a heritable mutation in DNA.²⁵ This alters the growth characteristics of a previously normal cell, which, in the case of colorectal cancer, results in an abnormally proliferating focus of cells that is morphologically identifiable as an adenomatous polyp. These abnormally proliferating but still "benign" cells are predisposed to undergoing further genetic changes that may result in cells with an overtly malignant phenotype. This multistep theory of colorectal carcinogenesis implies two major concepts: that colorectal adenomas are premalignant lesions and that malignant lesions should have more genetic abnormalities than premalignant lesions. I will explore each of these points briefly.

TABLE 1.—Possible Dietary Components in Colorectal Carcinogenesis

Protective Effects	Increases Risk
Fiber	Fat intake
Calcium	Folate deficiency
Salicylates	Carcinogen ingestion
Vitamins A, C, and E	

TABLE 2.—Modified Dukes' Classification for Colorectal Cancer* With 5-Year Survival by Stage†

Dukes' Stage	Extent of Tumors	5-Year Survival, %
A	Limited to submucosa	90-95
B	Into muscular layers of the colon	
B1	Into muscularis propria; no nodal metastases	90
B2	Through serosa; no nodal metastases	75
C	Regional nodal metastases	
C1	1-4 regional nodes	65
C2	>4 regional nodes	42
D	Distant metastases	>5

*From Turnbull.¹⁸
†From Newland et al.,¹⁹ Turnbull et al.,²⁰ and the Gastrointestinal Tumor Study Group.²¹ Some surgical series report different survival figures (Moertel et al²²).

The first point is the so-called adenoma-carcinoma hypothesis. Evidence from epidemiologic studies of sporadically occurring colonic adenomas and carcinomas and familial polyposis syndromes strongly suggests that adenomas precede carcinomas by five to ten years.^{15,26} Histologic studies show a continuum of increasing polyp size and dysplasia from simple tubular adenomas to malignant neoplasms that correlates well with an increasing risk of containing malignant foci (Table 3).²⁹ These findings, along with the frequent coexistence of adenomatous and malignant tissue within the same lesion, add considerable weight to this hypothesis.²⁷⁻²⁹

Thus, if colorectal adenomas are precursors to carcinoma, then proving this hypothesis would appear to be relatively straightforward; that is, the removal of adenomas should markedly decrease the incidence of colorectal cancer. The idea, however, that adenomas are premalignant lesions has gained such strong support that it is considered unethical to have a study group in which adenomas are not removed. As a result, investigators have had to use historical data to determine the expected number of colon cancers in a given population as a control group. Patient selection in these studies has also been criticized. With that in mind, studies have shown that removing all polyps decreases the expected rate of rectal cancer development by 70% (polypectomies during rigid sigmoidoscopy)³⁰ and that of colorectal cancer by 57% to 87% (polypectomies during total colonoscopy).³¹ Thus, the evidence strongly supports the theory that adenomas are premalignant lesions. Malignant lesions arising in patients with inflammatory bowel disease, the flat adenoma syndrome,³² and HNPCC may not have a clear adenomatous polyp phase. These conditions make up a small percentage of the total number of cases of colorectal cancer, however.

Molecular Genetic Events in Colorectal Carcinogenesis

Molecular studies of the roles played by oncogenes and tumor suppressors during cell replication clearly indicate that replication is controlled at several levels extend-

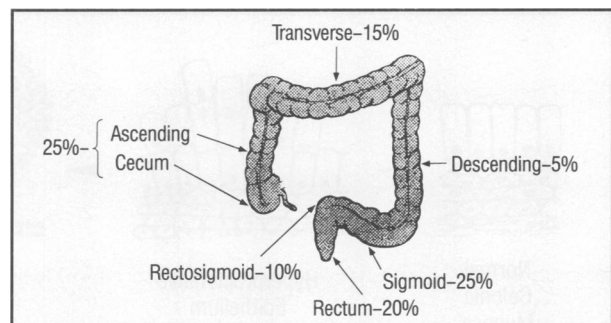


Figure 2.—The schematic shows the distribution of colorectal cancers.

ing from the external cellular milieu to the innermost parts of the nucleus. Because the multistep theory of carcinogenesis predicts that as a cell proceeds toward malignancy, a number of genetic alterations will occur, it follows that these alterations would occur in proteins that are control points for cellular replication.²⁵ A process as vital—and, if uncontrolled, possibly lethal—as cell replication would be expected to have controls at several levels, and the most commonly held view is that the key proteins at these control points are proto-oncogenes and tumor suppressors. The multitude of proto-oncogenes or tumor suppressors currently known suggests that the number, chronology, and identity of these genetic alterations need not be the same in each neoplasm, but that, overall, malignant lesions should have more mutations than premalignant lesions. Because of fiberoptic technology, it has become relatively easy to obtain fresh specimens from all stages of colorectal cancer development, making studies of the genetic changes occurring during carcinogenesis possible.

In a landmark study, Vogelstein and co-workers examined the frequency of several genetic alterations known to be present in many colon cancers, that is, *ras* gene mutations and chromosomal deletions on 5q (adenomatous polyposis coli gene, which is mutated in both familial adenomatous polyposis [FAP] and Gardner's syndrome), 18q (*DCC* ["deleted in colon cancer"]), and 17p (*P53*), and correlated these alterations with their "position" in the adenoma-carcinoma sequence.³³ Their data suggested that a general chronologic order of genetic alterations can be made—that is, 5q, *ras*, 18q, 17p (Figure 3),^{33,34} although the order was by no means invariable; and that a strict chronologic order of genetic alterations is not as important as their accumulation in the development of colorectal cancer (Figure 4). Subsequent work in experimental systems has suggested that correcting the defects in tumor suppressor genes will inhibit tumorigenicity.^{35,36}

Because knowledge regarding the genetic changes involved in colorectal carcinogenesis has been accumulating so rapidly, it is easy to forget that the story is far from complete. Recently regions on chromosomes 2 and 3 have been linked with most of the HNPCC kindreds.³⁷⁻⁴¹ Hereditary nonpolyposis colorectal cancer is strongly associated with a phenotypic pattern of genomic instabil-

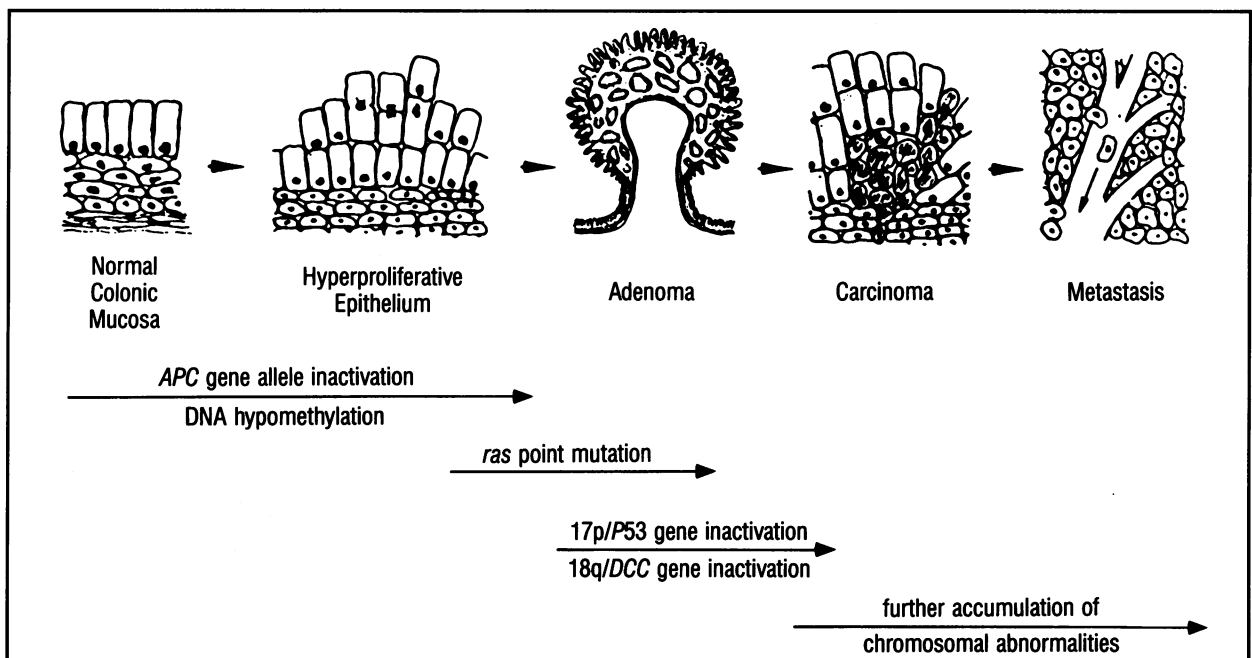


Figure 3.—Genetic alterations are shown during the adenoma-carcinoma sequence. Although this graph shows the most common chronology, the accumulation of abnormalities rather than their specific order is probably more important in developing the malignant phenotype (from Vogelstein et al³³; reproduced from Bresalier and Toribara³⁴ with permission from the authors, WB Saunders Company, and Appleton & Lange Publishing Company).

ity in the DNA of the cancers, that is, replication errors. This pattern is also present in the tumors of approximately 15% of persons having “sporadic cancers,” suggesting that this abnormality may play a role considerably beyond the classic HNPCC families.^{37,42,43} Candidate genes designated *hMSH2* (chromosome 2) and *hMLH1* (chromosome 3) are the human homologues to DNA repair enzymes found in *Escherichia coli* and yeast that are known experimentally to cause a similar pattern of genomic instability.^{38,39,44} Thus, although their role in the progression to cancer has not yet been defined, many investigators feel

that the discovery of these genes may yield clues to the genetic instability that characterizes colon carcinogenesis, both in familial and in sporadic colon cancers. Knowledge about the possible functions of the other genes involved in colon carcinogenesis is also accumulating. The tumor suppressor gene *P53* appears to be involved in ensuring DNA fidelity by controlling the progression of cells through the cell cycle⁴⁵ whereas *APC* and *DCC* gene products may be involved in cell-cell interactions (such as contact inhibition),^{46,47} and *ras* may be involved in growth signal transduction.⁴⁸ Other such discoveries will undoubtedly be forthcoming from these molecular genetics studies.

Screening for the Early Detection of Colorectal Cancer

Screening for colorectal cancer is an area of both progress and controversy. The rationale for developing a screening program is clear. Colorectal cancer is a substantial health problem that is potentially preventable in a premalignant stage (given the therapeutic capabilities of fiberoptic endoscopy) or curable in the early stages of malignancy by surgical treatment. The primary prevention of malignancy is not possible because the agents that are responsible for initiating the malignant process have not yet been identified. Therefore, the goal of a colorectal cancer screening program is to improve morbidity and mortality by allowing neoplasms to be identified at a premalignant or potentially curable malignant stage while maintaining patient acceptability and treatment cost-effectiveness. Because screening the entire United States

TABLE 3.—Risk of Carcinoma by Adenoma Size, Histologic Type, and Degree of Dysplasia*

Risk Factor	Patients With Carcinoma, %
Adenoma size, cm	
<1	1.3
1 to 2	9.5
>2	46.0
Histologic type	
Tubular	4.8
Tubulovillous	22.5
Villous	40.7
Degree of dysplasia	
Mild	5.7
Moderate	18.0
Severe	34.5

*Adapted from Itzkowitz and Kim.²⁹

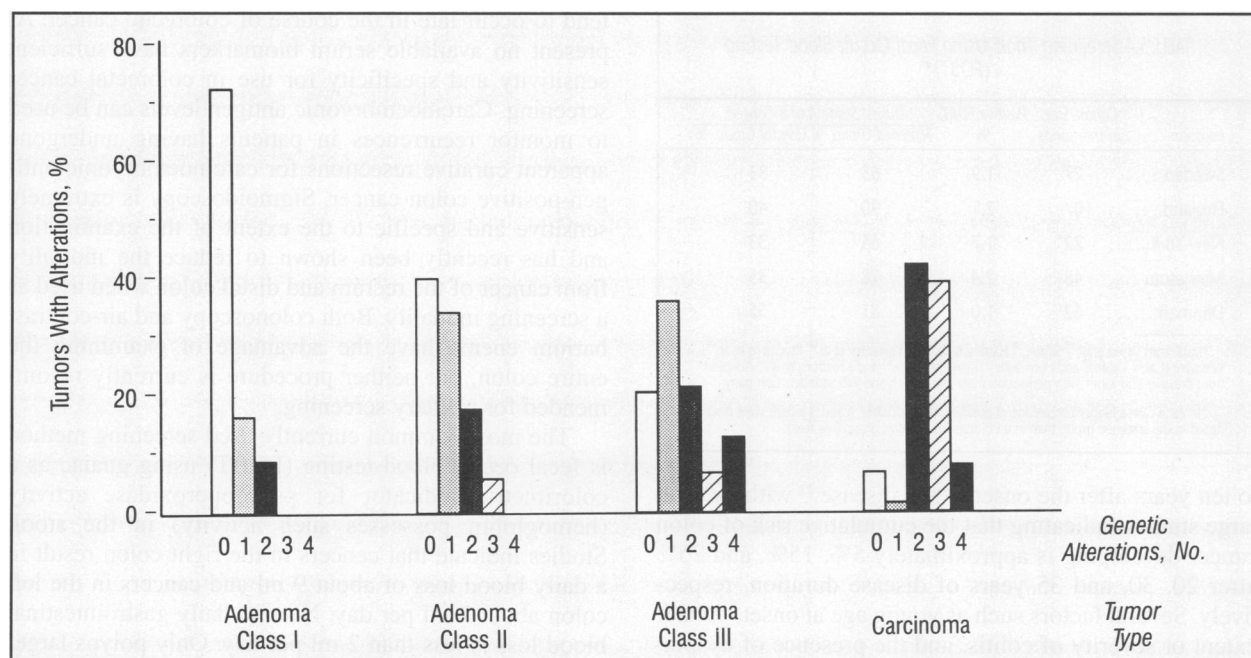


Figure 4.—The accumulation of genetic alterations (*ras* point mutations, 17p/*P53*, 18q/*DCC*, and 5q/*APC* deletions) is shown as a function of position in the adenoma-carcinoma spectrum (adapted from Vogelstein et al³³ with permission from the authors and the Massachusetts Medical Society).

population is not practical, the identification of subgroups at increased risk for colorectal cancer is important.

Table 4 lists some of the risk factors approximately in order of increasing risk of colorectal cancer developing. Age itself is a risk factor.²⁴ Before age 40, the incidence of colorectal cancer in the general population is less than 1 per 100,000. This incidence then begins to rise and roughly doubles with each decade after age 50, reaching almost 500 per 100,000 by age 80. Having a single first-degree relative with colorectal neoplasm(s)⁴⁹ or a history of genitourinary or breast cancer carries a slightly increased risk for colon cancer, perhaps on the order of 1.5- to 2-fold over the general population. Whether this slightly increased risk is due to the inclusion of patients with HNPCC (Lynch II syndrome) or truly represents an increased risk for sporadic adenomas and carcinomas is not clear.

Several conditions are listed as conferring a moderately increased risk for colon cancer. These include Crohn's disease,⁵⁰ having two first-degree relatives with colorectal cancer,¹⁶ and having had colorectal cancer.¹⁷ Inflammatory bowel disease, specifically ulcerative colitis, has traditionally been associated with an increased risk for colorectal cancer. More recently, it has been recognized that patients with Crohn's colitis are also at increased risk, although at a longer duration of disease and lower incidence than with ulcerative colitis, perhaps because the proportion of involved colonic mucosa in patients with Crohn's colitis is usually lower than with ulcerative colitis. Epidemiologic studies suggest that patients with two first-degree relatives, although not necessarily meeting the strict criteria for HNPCC (dis-

cussed later), may have a fivefold to sixfold higher risk of colon cancer developing than a "normal" population. There is also evidence that the development of so-called sporadic adenomatous polyps has an inherited component.⁵¹ Patients with previous adenomatous polyps are also thought to be at a moderately increased risk if their polyps were multiple, larger than 1 cm, or had an unfavorable cellular pattern—that is, moderate to severe atypia or carcinoma in situ. Surprisingly, a previous colon cancer does not seem to confer a substantially greater risk for colorectal cancer than having a large adenoma or one with an unfavorable histologic type, unless other neoplasms are present at the time of diagnosis.²⁴

A number of conditions are associated with a high risk for colon cancer. Ulcerative colitis increases the risk of colorectal cancer, although the magnitude of the risk is not known with certainty. The risk begins to rise seven

TABLE 4.—Patient Characteristics of Those at Increased Risk (Mild, Moderate, or High) for Colorectal Cancer

Increased Risk	Patient Characteristic
Mild	Age over 40 First-degree relative with colorectal neoplasm History of genitourinary or breast cancer
Moderate	Crohn's disease Previous colon cancer Previous adenomatous polyps (multiple, large, or high degree of dysplasia)
High	2 First-degree relatives with colon cancer Ulcerative colitis (long duration) Hereditary nonpolyposis colon cancer Familial adenomatous polyposis or Gardner's syndrome

TABLE 5.—Screening Trials Using Fecal Occult Blood Testing (FOBT)*

Location	Cohort Size, in thousands	Positive FOBT, %	Dukes' Stage A or B Cancer Screened Group, % Control Group, %	
Sweden	27	1.9	65	33
England	107	2.1	90	40
New York	22	1.7	65	33
Minnesota	48	2.4	78	35
Denmark	62	1.0	81	55

*Data from Vasen et al,⁵⁷ Simon,⁵⁸ Hardcastle et al,⁵⁹ Kewenter et al,⁶⁰ Kronborg et al,⁶¹ Winawer et al,⁶² Thomas and Hardcastle,⁶⁴ Kewenter et al,⁶⁵ and Kronborg et al.⁶⁶ Adapted from Bresalier and Kim¹⁷ with permission from the authors and WB Saunders Company.

†In each case a higher percentage of possibly curable Dukes' A and B lesions were diagnosed in the screened group than in an unscreened control group (see text).

to ten years after the onset of the disease,⁵² with several large studies indicating that the cumulative risk of colon cancer developing is approximately 5%, 15%, and 25% after 20, 30, and 35 years of disease duration, respectively. Several factors such as young age at onset, greater extent or severity of colitis, and the presence of dysplasia on initial surveillance colonoscopy may define subpopulations at increased risk for colorectal cancer.⁵³⁻⁵⁶ Familial adenomatous polyposis and Gardner's syndrome are autosomal dominantly inherited syndromes linked to abnormalities in the *APC* gene in which colon cancer will develop in virtually 100% of affected patients without intervention.

The realization that more colonic neoplasms have a hereditary component than was previously thought has fueled interest in HNPCC (including Lynch syndromes I and II). This hereditary syndrome until recently was defined solely by strict historical criteria:

- Three or more relatives have histologically verified colorectal cancer, one of whom is a first-degree relative of the other two;
- Colorectal cancer involves at least two generations; and
- One or more colorectal cancer cases are diagnosed before age 50.⁵⁷

Using these strict criteria may well underestimate the prevalence of HNPCC, however, because some families with a clear predilection for colon cancer do not meet all of these criteria. The recently described genetic defects on chromosomes 2 and 3 appear to be the abnormality present in most of these kindreds.^{37,42} The fact that a substantial number of HNPCC families are not linked to these two genetic loci indicates that this syndrome may be caused by several different genetic abnormalities that may differ in their clinical characteristics and genetic penetrance.

What methods can be used for screening? A careful history can uncover previous polyps or cancer as well as a genetic predisposition. Physical examination is rarely helpful, particularly with the shift of colonic neoplasms toward the right colon. Symptoms are nonspecific and

tend to occur late in the course of colorectal cancer. At present no available serum biomarkers have sufficient sensitivity and specificity for use in colorectal cancer screening. Carcinoembryonic antigen levels can be used to monitor recurrences in patients having undergone apparent curative resections for carcinoembryonic antigen-positive colon cancer. Sigmoidoscopy is extremely sensitive and specific to the extent of the examination and has recently been shown to reduce the mortality from cancer of the rectum and distal colon when used as a screening modality. Both colonoscopy and air-contrast barium enema have the advantage of examining the entire colon, but neither procedure is currently recommended for primary screening.

The most common currently used screening method is fecal occult blood testing (FOBT) using guaiac as a colorimetric indicator for pseudoperoxidase activity (hemoglobin possesses such activity) in the stool. Studies indicate that cancers in the right colon result in a daily blood loss of about 9 ml and cancers in the left colon about 2 ml per day. Normal daily gastrointestinal blood loss is less than 2 ml per day. Only polyps larger than 1.5 cm in diameter consistently cause a blood loss of more than 2 ml per day.⁵⁸ In theory, it should be possible to identify most patients with colon cancer and some with large polyps by examining the stool for abnormal amounts of blood. In practice, however, dietary factors and noncolonic blood loss into the gastrointestinal tract cause a considerable number of false-positive tests, particularly when the tests are adjusted to detect blood loss near the 2-ml-per-day level. Nonhydrated guaiac-based FOBTs will give positive results in about 2% of the population (Table 5)^{17,59-66} while missing about 40% of colon cancers and 60% of polyps greater than 1 cm in size.⁶⁷ Workups for positive FOBTs will yield no disease in about 50% of cases. Immunologic tests (specific for human hemoglobin) could improve the specificity of a positive FOBT, and preliminary results have been somewhat encouraging. Another possible approach to improving the specificity of FOBT might be the use of a two-tiered system of testing.⁶⁷ Even small improvements in specificity could have a major influence on cost-effectiveness when one considers screening programs involving millions of people.

Having presented the disadvantages of fecal occult blood testing, we might ask whether screening using FOBT is effective in decreasing mortality from colon cancer. A number of large trials have suggested that a higher percentage of colorectal cancers in the screened population will be discovered in patients with stage A or B cancer than in unscreened controls—that is, in stages where the cancers have a relatively high chance of cure (Table 5). Two recent studies have also indicated that annual FOBT screening decreases the mortality from colorectal cancer by as much as 33%.^{68,69} Given these results, arguments opposing the use of FOBT as a screening modality on the basis of a lack of proven efficacy have been weakened. The major criticism remain-

ing is the cost efficiency of such screening. Although such complex analysis is beyond the scope of this discussion, at least one computer analysis of this issue suggested that the cost per year of life saved (using the data compiled by Mandel and associates⁶⁸) compares favorably with the figures for breast cancer screening for women older than 50 years.⁷⁰

Several other screening modalities have been proposed recently. Hydrocolonic sonography has been suggested as a possible alternative or adjunctive method for visualizing the colon.⁷¹ Applying molecular biologic techniques may yield a new generation of screening tests. The polymerase chain reaction can be used to directly detect *ras* oncogene mutations in the DNA from cells shed into the bowel lumen by neoplasms⁷² and in combination with other molecular techniques can detect most *APC* mutations without requiring the sequencing of the entire gene.⁷³ *P53* and *DCC* abnormalities may serve as adjunctive tests for determining the prognosis and therapy after the diagnosis of colon cancer, but they occur late in the progression to cancer.^{74,75} Even though none of the currently known genetic abnormalities appear to be useful for general screening purposes, the available technology can be easily adapted for clinical purposes.

At this point, it is probably not useful to discuss specific screening strategies, as there is no clear consensus on what is the optimum method(s), timing, or interval to use. Several observations should be made, however. Perhaps the most important point is that more frequent screening or surveillance is not necessarily better. For example, a recent article showing the efficacy of sigmoidoscopy in decreasing mortality from colorectal cancer also showed that this protective effect extended as long as ten years after the sigmoidoscopy, which is twice the interval recommended by the American Cancer Society.⁷⁶ Fecal occult blood testing, if used for screening, should be done annually. The occurrence of a single adenoma in a patient has often been used to justify repeated annual surveillance examinations. Recent studies, however, have indicated that patients with single adenomas smaller than 1 cm do not have a substantially higher risk for subsequent colonic neoplasms when compared with the rest of the population and therefore do not need an intensive surveillance regimen.^{77,78} Surveillance is indicated for patients with a history of adenomas that are large, multiple, or have unfavorable histologic features (tubulovillous or villous adenomas or moderate to severe atypia) because these patients appear to be at increased risk of having subsequent adenomas and cancers. The optimum surveillance interval has not yet been determined, but almost certainly need not be more frequent than every three years once the colon has been cleared of polyps and the mucosa has been adequately visualized.⁷⁹ More frequent visualization may be indicated in patients with malignant polyps (when a malignant focus has invaded into the muscularis propria), sessile adenomas, or a strong family history.

Summary and Conclusions

A large body of information supports the adenoma-carcinoma hypothesis. These data suggest that for most colorectal carcinomas, the time course for the development of malignancy from previously normal mucosa is about ten years. Removing adenomas decreases the risk of malignancy subsequently developing, and discovering colorectal cancers at earlier stages decreases the mortality. Screening programs are of arguable cost-effectiveness, but they do appear to increase the percentage of colorectal cancers that are discovered in earlier stages as well as decreasing the mortality of colorectal cancer within the screened population. Screening programs should employ 60-cm flexible sigmoidoscopy—this procedure is not appropriate in patients with HNPCC or inflammatory bowel disease, however—with or without the addition of FOBT. The use of FOBT is somewhat controversial because of the marginal sensitivity and specificity of the tests currently available. It is hoped that technologic innovations and molecular biologic discoveries will allow the development of better screening modalities and that epidemiologic studies will result in the identification of factors that lead to primary prevention.

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